Glycemia, hypoglycemia, and costs of simultaneous islet-kidney or islet after kidney transplantation versus intensive insulin therapy and waiting list for islet transplantation

Gerber, Philipp A ; Locher, Rebecca ; Zuellig, Richard A ; Tschopp, Oliver ; Ajdler-Schaeffler, Evelyne ; Kron, Philipp ; Oberkofler, Christian ; Brändle, Michael ; Spinas, Giatgen A ; Lehmann, Roger

Abstract: BACKGROUND: Long-term data of patients with type 1 diabetes mellitus (T1D) after simultaneous islet-kidney (SIK) or islet-after-kidney transplantation (IAK) are rare and have never been compared to intensified insulin therapy (IIT). METHODS: Twenty-two patients with T1D and end-stage renal failure undergoing islet transplantation were compared to 70 patients matched for age and diabetes duration treated with IIT and to 13 patients with kidney transplantation alone or simultaneous pancreas-kidney after loss of pancreas function (waiting list for IAK [WLI]). Glycemic control, severe hypoglycemia, insulin requirement, and direct medical costs were analyzed. RESULTS: Glycated hemoglobin decreased significantly from 8.2 ± 1.5 to 6.7 ± 0.9% at the end of follow-up (mean 7.2 ± 2.5 years) in the SIK/IAK and remained constant in IIT (7.8 ± 1.0% and 7.6 ± 1.0) and WLI (7.8 ± 0.8 and 7.9 ± 1.0%). Daily insulin requirement decreased from 0.53 ± 0.15 to 0.29 ± 0.26 U/kg and remained constant in IIT (0.59 ± 0.19 and 0.58 ± 0.23 U/kg) and in WLI (0.76 ± 0.28 and 0.73 ± 0.11 U/kg). Severe hypoglycemia dropped in SIK/IAK from 4.5 ± 9.7 to 0.3 ± 0.7/patient-year and remained constant in IIT (0.1 ± 0.7 and 0.2 ± 0.8/patient-year). Detailed cost analysis revealed US $57,525 of additional cost for islet transplantation 5 years after transplantation. Based on a 5- and 10-year analysis, cost neutrality is assumed to be achieved 15 years after transplantation. CONCLUSIONS: This long-term cohort with more than 7 years of follow-up shows that glycemic control in patients with T1D after SIK/IAK transplant

DOI: https://doi.org/10.1097/TP.0000000000000720

Glycemia, Hypoglycemia, and Costs of Simultaneous Islet-Kidney or Islet After Kidney Transplantation Versus Intensive Insulin Therapy and Waiting List for Islet Transplantation

Philipp A. Gerber,[1] Rebecca Locher,[1] Richard A. Zuellig,[1] Oliver Tschopp,[1] Evelyne Ajdler-Schaeffler,[1] Philipp Kron,[2] Christian Oberkofler,[2] Michael Brändle,[3] Giatgen A. Spinas,[1] and Roger Lehmann[1]

Background. Long-term data of patients with type 1 diabetes mellitus (T1D) after simultaneous islet-kidney (SIK) or islet-after-kidney transplantation (IAK) are rare and have never been compared to intensified insulin therapy (IIT). **Methods.** Twenty-two patients with T1D and end-stage renal failure undergoing islet transplantation were compared to 70 patients matched for age and diabetes duration treated with IIT and to 13 patients with kidney transplantation alone or simultaneous pancreas-kidney after loss of pancreas function (waiting list for IAK [WLI]). Glycemic control, severe hypoglycemia, insulin requirement, and direct medical costs were analyzed. **Results.** Glycated hemoglobin decreased significantly from 8.2 ± 1.5 to 6.7 ± 0.9% at the end of follow-up (mean 7.2 ± 2.5 years) in the SIK/IAK and remained constant in IIT (7.8 ± 1.0% and 7.6 ± 1.0) and WLI (7.8 ± 0.8 and 7.9 ± 1.0%). Daily insulin requirement decreased from 0.53 ± 0.15 to 0.29 ± 0.26 U/kg and remained constant in IIT (0.59 ± 0.19 and 0.58 ± 0.23 U/kg) and in WLI (0.76 ± 0.28 and 0.73 ± 0.11 U/kg). Severe hypoglycemia dropped in SIK/IAK from 4.5 ± 9.7 to 0.3 ± 0.7/patient-year and remained constant in IIT (0.1 ± 0.7 and 0.2 ± 0.8/patient-year). Detailed cost analysis revealed US $57,525 of additional cost for islet transplantation 5 years after transplantation. Based on a 5- and 10-year analysis, cost neutrality is assumed to be achieved 15 years after transplantation. **Conclusions.** This long-term cohort with more than 7 years of follow-up shows that glycemic control in patients with T1D after SIK/IAK transplantation improved, and the rate of severe hypoglycemia decreased significantly as compared to control groups. Cost analysis revealed that islet transplantation is estimated to be cost neutral at 15 years after transplantation.

(*Transplantation* 2015;00: 00–00)

Diabetes mellitus type 1 (T1D) affects about 1 of 300 persons in Europe and the United States, and the incidence increased by 2% to 5% worldwide in the last decades.[1] The level of glycemic control necessary to prevent diabetes-related late complications as demonstrated by the DCC trial is often difficult to achieve without a concomitant increase in severe hypoglycemic episodes.[2] Even though the occurrence of diabetes-related complications could be reduced substantially over the last decade,[3,4] they are still the main cause of morbidity and mortality in patients with T1D.[1] Therefore, despite several therapeutic options that already exist for patients with T1D, there is still a need for further therapeutic improvements regarding glycemic control, reduction of severe hypoglycemia, and prevention of late complications in these patients. Pancreas and islet transplantation are therapeutic options to achieve insulin independence and normoglycemia or good glycemic control with no or little additional insulin and avoidance of severe hypoglycemia.[5] Fioretto et al[6] reported an improvement of diabetic nephropathy with dissolving of typical diabetic renal lesions 10 years after pancreas transplantation. A recent study described a deceleration of kidney function decline and diabetic retinopathy progression after islet transplantation.[7]

The main disadvantage of pancreas transplantation is the surgical risk with a high rate of perioperative and

Received 15 August 2014. Revision requested 16 January 2015.

Accepted 30 January 2015.

[1] Division of Endocrinology, Diabetes and Clinical Nutrition, University Hospital Zurich, Switzerland.

[2] Division of Transplantation Surgery, University Hospital Zurich, Switzerland.

[3] Division of Endocrinology, Diabetology and Osteology, Cantonal Hospital of St. Gallen, Switzerland.

The authors declare no funding or conflicts of interest.

P.A.G. and R. Locher contributed equally to this article.

P.A.G. participated in research design, performance of the research, data analysis, writing of the article. R. Locher participated in the performance of the research, data analysis, writing of the article. R.A.Z. participated in the performance of the research. O.T. participated in the performance of the research. E.A.-S. participated in the performance of the research and writing of the article. P.K, participated in data analysis and writing of the article. C.O. participated in data analysis and writing of the article. M.B. participated in research design and data analysis. G.A.S. participated in research design and writing of the article. R. Lehmann participated in research design, performance of the research, data analysis, and writing of the article.

Correspondence: Roger Lehmann, MD, Division of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland. (roger.lehmann@usz.ch)

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantjournal.com).

ISSN: 0041-1337/15/0000-00

DOI: 10.1097/TP.0000000000000720

postoperative complications. Despite improvements in the procedure and in the outcome of pancreas transplantation, the complication rate caused by perioperative bleeding, infections, anastomotic leakage, and thrombotic complications is still high and associated with serious consequences, such as pancreatectomy and intestinal involution. In a recent study by Perez-Saez et al,[8] more than 75% of pancreas recipients experienced an infection in the early postoperative period, nearly one third underwent reoperation primarily because of bleeding or infection, and about 20% experienced an acute rejection episode.

Islet transplantation represents a much safer method compared to whole pancreas transplantation.[9] In the past 2 decades, the isolation technique has been improved, and better immunosuppression protocols have been established, permitting improved results in islet transplantation.[10,11] At present, simultaneous islet-kidney (SIK) or islet-after-kidney (IAK) transplantation are established treatment options for patients with T1D and reimbursed by the health care system in some countries, including Switzerland.

Several studies[12-17] have documented improved glycemic control and less hypoglycemic episodes in the setting of islet transplantation alone (ITA).[11,12,15,17] However, little is known about long-term glycemic control after SIK or IAK transplantation in comparison to standard intensified insulin treatment (IIT). Only a few follow-up studies have assessed the outcome of islet transplantation beyond five years. Two studies assessed the outcome of ITA in 65[16] and ITA/IAK in 677 recipients[18] after 5 and 11 years, respectively, but the outcomes have not been compared to best medical treatment. Furthermore, there are only few data on cardiovascular risk factors like hypertension, lipids, or body weight. Therefore, long-term studies are necessary to compare glycemic control, occurrence of hypoglycemia, diabetes-related complications, and life expectancy in patients with SIK or IAK transplantation in comparison to patients with optimal insulin substitution and good glycemic control.

In the present study, patients with T1D after SIK or IAK transplantation were compared with a matched control group of patients receiving IIT (insulin pump or multiple daily insulin injections = IIT group) who were treated by the same physicians with regard to glycemic control, hypoglycemia rate, and insulin dose. Because immunosuppression has some impact on glycemic control, a group of patients with kidney transplantation alone (KTA) or patients after simultaneous pancreas-kidney (SPK) with loss of pancreas function were compared to the islet transplantation group.

MATERIALS AND METHODS

Study Design

Patients with T1D and no detectable C-peptide or C-peptide < 100 pmol/L who underwent islet transplantation at the University Hospital of Zurich from June 2000 until December 2009 were included: 15 patients with SIK, 6 patients with IAK, and 1 patient with islet after heart transplantation. One patient who died shortly after SIK transplantation (death not related to the transplantation) was excluded because of the missing follow-up. Follow-up ended on December 2013. Data were prospectively collected in a database und retrospectively analyzed and compared to a control group consisting of 70 patients, matched for sex, age, and diabetes duration, who were treated with intensive insulin therapy (IIT, insulin pump or multiple daily injections) by the same team of physicians (diabetologists) as patients receiving islet transplantation. For comparison of glycated hemoglobin (HbA1c) levels and insulin requirement, a second control group was added consisting of 13 patients with type 1 diabetes mellitus after KTA, or patients after SPK transplantation with loss of pancreas function and consecutive pancreas explantation. Both were on the waiting list for islet transplantation). Primary end points were HbA1c and incidence of severe hypoglycemia, the secondary endpoint was the daily insulin dose and direct medical costs.

Islet transplantation and data collection were performed according to a clinical protocol approved by the ethical committee of the Canton of Zurich (protocol number 721), and a written informed consent was signed by each patient.

Assessment of Islet Function, Glycemic Control, Hypoglycemia, and Cardiovascular Risk Factors

Insulin dose and HbA1c were determined every 3 months, and C-peptide in the islet transplant group for the first year every 3 months and yearly thereafter.

To assess the incidence of severe hypoglycemia, which was defined according to the American Diabetes Association criteria (requiring assistance or unconsciousness), patients were interviewed at each visit, and the episodes of severe hypoglycemia were recorded in the patient charts.

Cardiovascular risk factors, such as body weight, blood pressure (BP), and heart rate, were assessed every 3 months; total cholesterol, high-density cholesterol, low-density cholesterol (LDL), and triglyceride were measured every year.

Glucose self-measurements were assessed by analyzing glucose meter data with DIABASS 5 software (mediaspects, Konstanz, Germany).

Biochemical Analyses

The HbA1c was measured with the DCA 2000 (Bayer Diagnostics, Elkhart) according to the manufacturer's instructions. Plasma C-peptide was measured with an IRMA kit (Technogenetics, CIS Bio International, Schering, Baar, Switzerland) with a local laboratory intra-assay and interassay coefficient of variation of 4.7% and 5.6%, respectively, and a lower limit of detection of 12 pmol/L. Insulin was determined with a radioimmunoassay (Insulin-CT, CIS Bio International, Schering AG, Baar, Switzerland) with a local laboratory intra-assay and interassay coefficient of variation of 6.0 % and 7.9%, respectively, and a lower limit of detection of 10 pmol/L. Cholesterol was measured by an enzymatic colorimetric test using cholesterol esterase and cholesterol oxidase, triglycerides were determined by a colorimetric reaction with iodonitrotetazolium chloride after enzymatic hydrolysis (modular P lab analyzer, Roche, Switzerland). High-density cholesterol was measured by a homogeneous enzymatic test (Cobas Integra lab analyzer, Roche, Switzerland). The LDL was calculated with the Friedewald formula.[19]

Transplantation Procedure

Organ Retrieval

Pancreata were explanted from brain-dead multiorgan donors in different hospitals in Switzerland and centrally allocated (Swisstransplant, Bern, Switzerland). In recipients, written informed consent was given by the patient

TABLE 1.

Baseline patient characteristics

Parameter	Transplanted group (n = 22)	IIT group (n = 40)	Waiting list group[a] (n = 13)
Age (± SD), y	52.6 ± 8.8	53.1 ± 10.2	47.3 ± 9.5
Sex (male), %	56.5	54.3	61.5
BMI (± SD), kg/m^2	23.2 ± 3.7	25.8.0 ± 4.9[b]	24.4 ± 4.6
Diabetes duration (± SD), y	39.5 ± 9.1	38.2 ± 6.5	34.5 ± 11.7
HbA1c (± SD), %	8.2 ± 1.5	7.8 ± 1.0	7.8 ± 0.8
Insulin dose (± SD), U/kg per day	0.53 ± 0.15	0.59 ± 0.19	0.76 ± 0.21[b]
Hypoglycemic episodes (± SD), number/y	4.5 ± 9.7	0.1 ± 0.7/y[b]	n/a

[a]Patients after kidney transplantation alone or after SPK with pancreas transplant explantation on the waiting list for islet transplantation.
[b]Significantly different from transplanted group, $P < 0.05$.

beforehand. A negative complement-dependent cytotoxicity crossmatch between donor and recipient was required, as well as ABO compatibility.

Islet Isolation and Transplantation

Islet isolation and transplantation of the pancreatic islets were performed as described previously.[20] The transplanted islet volume as defined by islet equivalents (IEQ), the number of islets, and the isolation index were recorded. The concurrent kidney transplantation was performed in all patients heterotopically with transplantation of the graft into the right or left iliac fossa.

Indication for Retransplantation of Islets

The HbA1c > 7.0% and reoccurrence of severe hypoglycemia. If this occurred, islet could be retransplanted at any time during the follow-up. Achievement of insulin independence was not the primary target, but achievement of good glycemic control and avoidance of severe hypoglycemia,[5] therefore patients with the longest follow-up will get in general more islet transplants.

Immunosuppression

Patients with SIK were treated with tacrolimus and rapamycin after an induction therapy with daclizumab according to the Edmonton protocol.[6] The target long-term levels were 7 to 10 μg/L for rapamycin and 3 to 6 μg/L trough levels for tacrolimus. The immunosuppressive therapy for patients receiving IAK was the usual immunosuppression for a kidney transplant, with cyclosporine (C_0 target levels 200-250 μg/L the first 3 months, thereafter 60-100 μg/L) or tacrolimus (trough levels, 10-15 μg/L for the first 3 months, thereafter 4-8 μg/L), and mycophenolate mofetil (1000 mg twice per day if body weight >50 kg). The induction therapy consisted of daclizumab (1 mg/kg on day 0, and q14 days for a total of 5 doses) or basiliximab (20 mg on days 0 and 4). They had either no steroids, or for patients after kidney transplantation a maximum of 5 mg prednisone, which was discontinued after 6 months.

Cost Assessment

Costs are given in US dollar and Swiss Francs (CHF) in parentheses, based on the exchange rate on January 14, 2015. Total costs for 1 islet transplantation (islet after kidney) was calculated by using the mean detailed cost of all islet transplantations performed during the last 5 years in our institution, which is $47,054 (46,222 CHF), respectively. Costs for islet isolation and infusion during SIK are $23,098 (22,690 CHF). Costs of 1 episode of severe hypoglycemia amount to $1074 (1055 CHF) (24). The average costs of insulin is $61.1 per 1000 units (60.0 CHF), 1 glucose test strip $0.92 (0.90 CHF), and yearly leasing costs for an insulin pump are $4013 (3942 CHF). Total costs were assessed before transplantation at 1, 5, and 10 years after transplantation. Costs of the transplanted group are compared to extrapolated cost without islet transplantation.

Data Analysis and Statistical Analysis

Data are given as mean ± SD and as median and lower/upper quartiles where appropriate. For comparison of continuous variables between 2 independent groups, the Mann-Whitney *U* test was used, for related samples, the Wilcoxon test was applied. A *P* value less than 0.05 was considered significant. The Bonferroni correction was used to account for multiple comparisons, and a *P* value less than 0.0055 was considered significant in the 8-year follow-up. For the analysis of categorical frequency data, the χ^2 procedure was applied.

RESULTS

Patient and Transplant Characteristics

Of the 22 patients with T1D receiving islet transplantation, 15 underwent SIK, 6 IAK, and 1 islet after heart transplantation. Baseline characteristics were not different with regard to age, sex, diabetes duration, HbA1c or daily insulin dose between transplant and control group, but the transplantation cohort had significantly more severe hypoglycemia episodes ($P < 0.001$) and a lower body mass index (BMI) ($P = 0.02$) compared to the control group (IIT group, Table 1). Patients in the control group had normal kidney function (creatinine clearance of 85.1 mL/min per 1.73 m^2). The mean follow-up was 7.2 ± 2.5 years.

Transplant characteristics including number of islet infusions and transplanted islet volume (total IEQ, IEQ/kg body weight) are shown in Table 2.

Glycemic Control and Incidence of Hypoglycemia

The HbA1c decreased significantly by 1.5% from baseline (8.2 ± 1.5%) to the end of follow-up (6.7 ± 0.9, $P < 0.001$) in the transplantation group and remained unchanged in the IIT group (7.8 ± 1.0% versus 7.6 ± 1.0%, ns) (Figure 1A). Similarly, HbA1c remained high (comparable to the IIT group) in patients on the islet transplantation waiting list or patients who received combined pancreas-kidney transplantation, but lost function of the transplanted pancreas (from 7.8 ± 0.8% to 7.9 ± 1.0% during follow-up, ns, Figure 1A).

TABLE 2.

Transplantation-related characteristics

Parameter	Median	Quartiles
Islet infusion (number)	2[a]	1.25/3.0
Total IEQ	532,786	411,220/1,185,250
IEQ/kg body weight	9893	5845/16,980
Cold ischemia time (h:min)	5:23	3:27/7:07

[a]Indication for retransplantation of islets: HbA1c > 7.0% and reoccurrence of severe hypoglycemia, and not insulin independence.

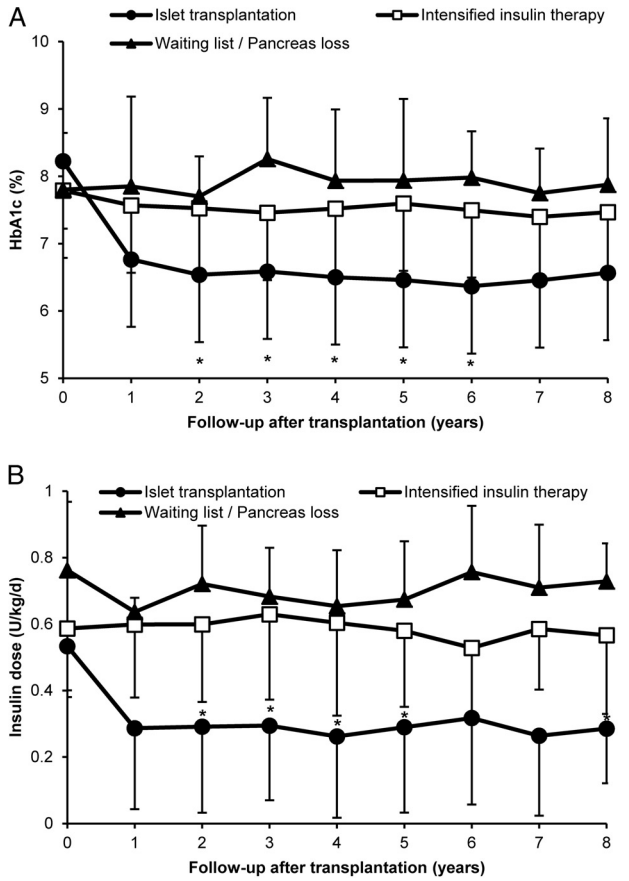

FIGURE 1. Mean HbA1c and daily insulin requirement. A, Mean HbA1c in the islet transplantation group compared to the matched control group treated with intensive insulin therapy, as well as compared to a control group of patients on the islet transplantation waiting list, or patients after simultaneous pancreas-kidney transplantation with loss of pancreas function and consecutive pancreas explantation during a follow-up of 8 years. A significant reduction from baseline to the end of follow-up was seen in the transplantation group ($P = 0.001$), but no change in the other groups (ns). B, Mean daily insulin dose (units) per kilogram and day compared between the three groups during a follow-up of 8 years. A significant reduction from baseline to the end of follow-up was seen in the transplantation group ($P = 0.03$), but no change in the other groups (ns). The two control groups did not differ with regard to HbA1c levels and insulin dose. *Significant difference ($P < 0.05$, adjusted for multiple comparisons) of HbA1c or insulin dose in the islet transplantation group compared to both other groups.

In the transplantation group, 50% of the 22 patients were treated with an insulin pump at baseline as compared to 29% in the control group ($P = 0.06$). After islet transplantation, only 7 of the 11 patients with an insulin pump therapy continued insulin pump treatment (included in the cost analysis).

Despite better glycemic control with lower HbA1c, the number of severe hypoglycemic episodes decreased from 4.5 ± 9.7 to 0.3 ± 0.7/yr ($P = 0.03$) in the transplantation group with no change of hypoglycemia rate in the control group (0.1 ± 0.7/yr versus 0.2 ± 0.8/yr, $P = 0.85$). On follow up, the number of severe hypoglycemia was similar in both groups (Figure 2).

Insulin Requirement

After islet transplantation, the daily insulin requirement dropped by nearly 50% from 0.53 ± 0.15U/kg/d at baseline to 0.33 ± 0.24U/kg ($P < 0.01$) and remained constant in the IIT (0.59 ± 0.19 and 0.58 ± 0.23U/kg) and in waitlist group (0.76 ± 0.28 and 0.73 ± 0.11 U/kg) at the end of follow-up (Figure 1B). Six patients became insulin-independent, with two of them remaining insulin-independent after 5 years. Because immunosuppression increases insulin resistance and insulin requirement, the daily insulin requirement after islet transplantation has to be compared to the waiting list group KTA or SPK after pancreas function loss.

Cardiovascular Risk Factors

The BMI showed a tendency towards a decrease in the transplantation group from 23.2 ± 3.7 kg/m^2 to 22.0 ± 3.1 kg/m^2 ($P = 0.058$), whereas there was no change in BMI in the IIT group during the follow-up (Table 3). Total cholesterol and LDL cholesterol decreased in both groups, without a significant difference at the end of follow-up. Systolic as well as diastolic BP decreased in both groups during follow-up. The use of antihypertensive and lipid-lowering medication differed between groups. Antihypertensive therapy was present at the beginning of follow-up in 77.3% and 48.6% of patients in the transplantation and IIT group, respectively ($P = 0.03$), and at the end of follow-up in 81.8% and 51.4% of patients in these groups ($P = 0.01$). Similarly, lipid-lowering therapy was taken in 68.2% (transplantation group) and 41.4% (ITT) of patients at the beginning of follow-up ($P = 0.05$), and in 72.7% and 47.1% of patients at the end of follow-up ($P = 0.05$).

Side Effects of Islet Transplantation

Two transplanted patients developed interstitial pneumonitis due to rapamycin treatment which was replaced by mycophenolate and two experienced capsular liver bleeds without requiring transfusion or surgery.

Costs

In Table 4, costs for insulin, insulin pump treatment, severe hypoglycemia (direct costs),[24] self glucose measurements as well as costs attributable to islet transplantations (isolations and infusions) and immunosuppression are listed based on the current results of this study. Costs of transplantation were calculated based on actual costs for hospitalization during transplantation, considering the number of SIK and IAK in the whole cohort, as described in Materials and methods

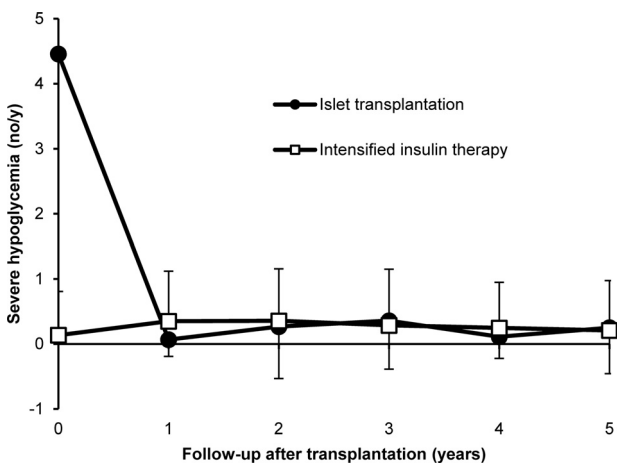

FIGURE 2. Hypoglycemia incidence. Rate of severe hypoglycemia per patient-year in the islet transplantation group compared to the matched control group, with a significant reduction in the transplantation group ($P = 0.03$), but no change in the IIT group ($P = 0.85$).

TABLE 3.

Cardiovascular risk factors

	Transplanted group	IIT group				
Parameter	Start	EFU[a]	Start	EFU	*P* Start	*P* EFU
Serum lipids (± SD), mmol/L						
Total cholesterol	5.1 ± 1.2	4.3 ± 1.0	5.1 ± 1.1	4.8 ± 1.0	0.48	0.06
HDL cholesterol	1.7 ± 0.5	1.6 ± 0.5	1.7 ± 0.5	1.8 ± 0.6	0.45	0.12
Triglycerides	1.3 ± 0.5	1.4 ± 1.3	1.3 ± 0.5	1.3 ± 0.8	0.68	0.57
LDL cholesterol	2.8 ± 1.0	2.3 ± 0.8	2.8 ± 0.8	2.5 ± 0.9	0.47	0.28
BP (± SD), mm Hg						
Systolic BP	147.7 ± 14	139.7 ± 21	136.4 ± 24	130.9 ± 20	0.006	0.09
Diastolic BP	82.8 ± 10	74.8 ± 12	78.7 ± 11	75.0 ± 8	0.06	0.9
BMI (± SD), kg/m^2						
BMI	23.2 ± 3.7	22.0 ± 3.1	25.8 ± 4.6	25.7 ± 4.4	0.021	0.001

[a]EFU = end of follow-up; HDL, high-density cholesterol.

section. Costs for immunosuppression are only included in the assessment of total costs for medication exceeding therapy in kidney only transplantation. Self-glucose measurements were reduced from 8 (frequent severe hypoglycemia) per day to 4 per day (estimation from downloaded blood glucose measurements in the Diabass Software) in the transplanted group, and insulin pump was discontinued in 4 of 11 patients because of good islet function.

DISCUSSION

Islet transplantation represents an effective and minimally invasive treatment option in selected patients with T1D. We previously showed that glycemic control after SIK or IAK is comparable to whole pancreas transplantation with a higher need for exogenous insulin, but a much lower rate of complications.[9] This single-center study with a follow-up of more than 7 years demonstrates that patients with T1D and a kidney transplant receiving islet transplantation achieve significantly better glycemic control as compared to an age, sex, and diabetes duration matched group of patients with T1D who were treated with best medical therapy. This decrease of HbA1c of 1.5% between baseline and end of follow-up and the difference of 0.9% as compared to the control group is relevant for prevention of late complications, in particular damage to the transplanted kidney.[2,21] Despite this significantly better A1c, the rate of severe hypoglycemia was reduced from 4 to 0.3 per patient year which is comparable to the rate in the control group.

The effect of islet transplantation on cardiovascular risk factors is not well known. Systolic as well as diastolic BP decreased in both groups during follow-up, most likely due to a multifactorial approach to treat patients with T1D and multiple complications by antihypertensive drugs, and if indicated with statins and aspirin. The use of antihypertensive and lipid lowering medication differed between groups. It can be assumed that certain factors in the transplantation group (as impairment of renal function or immunosuppressive therapy) may contribute to a higher rate of use of these medications. Indeed, we measured slightly higher BP values in the transplantation group compared to the ITT group (Table 3).

The examination of cardiovascular risk factors in our study revealed a BMI with a tendency to decrease in the transplantation group, most probably due to increased physical activity after kidney transplantation and less defensive eating to prevent hypoglycemias, whereas there was no change in BMI in the control group during follow-up. Further examinations with larger patient numbers and longer follow-up are necessary to test whether islet transplantation positively reduces the risk for cardiovascular events beyond better glycemic control. It is feasible that prevention of hypoglycemia in diabetes of long duration could reduce mortality by avoiding heart rhythm disturbances caused by long QT-interval and hypoglycemia.[22]

TABLE 4.

Estimated costs (US $) per patient of islet transplantation compared to continued intensive insulin treatment without transplantation

Direct Costs (US $)	Extrapolated costs without transplantation	After islet transplantation
First year		
Insulin pens	791	426
Insulin pump	2006	1275
Hypoglycemia	4832	353
Transplantation	0	59,612
Additional immunosuppression	0	696
Blood glucose measurements	2675	1336
Total cost	10,304	63,666
After 5 y		
Insulin	3959	2130
Insulin pump	10,030	6380
Hypoglycemia	24,163	1692
Transplantation	0	91,692
Additional immunosuppression	0	3480
Blood glucose measurements	13,375	6685
Total cost	51,527	111,981
After 10 y		
Insulin	7919	4259
Insulin pump	20,062	12,761
Hypoglycemia	48,325	3228
Transplantation	0	100,247
Additional immunosuppression	0	6969
Blood glucose measurements	26,752	13,371
Total cost	103,058	140,825

Exchange rate (January 14, 2015): 1 CHF = US $1.018.

Treatment of T1D and its complications poses a high economic burden. In addition to improvement of medical outcome and quality of life, islet transplantation may also have economic advantages. This study demonstrated that islet transplanted patients have a marked reduction in insulin requirement and hypoglycemic events. Because many of these patients with hypoglycemia unawareness are candidates for a continuous glucose measuring system (as of January 1, 2014, fully reimbursed in all patients with type 1 diabetes in Switzerland), the savings of islet transplantation may be even greater. Our study implies that islet transplantation may be cost-neutral after approximately 15 years. This is somewhat later compared to a recent economic analysis by Beckwith et al[23] demonstrating that ITA is more effective than standard insulin therapy and cost-saving at about 9 to 10 years after transplantation. However, at 10 years, we calculated costs for HbA1c—lowering by 1% to be $2502 per year, which we believe is an acceptable amount. Furthermore, if glucose control is insufficient—as shown in patients with KTA[9]—kidney function of the transplanted kidney might deteriorate much faster, requiring another kidney transplantation or dialysis at an earlier time point. Under these circumstances, the cost analysis might even be cost-saving. It should be mentioned that we did not include any cost for pancreas acquisition in our analysis because there are no such costs in Switzerland, and in most other countries that offer islet transplantation programs. However, there are countries where such costs have to be taken into account. An overview of these costs in different countries is provided in **Table S1** (**SDC**, http://links.lww.com/TP/B146). We also did not include costs for immunosuppression (except for immunosuppression exceeding the therapy after kidney transplantation), complications of immunosuppression or their prevention, because these costs are assumed to be similar for kidney (or heart) transplantation alone. Finally, there are no costs for transplantation monitoring because specific monitoring of islet function does not differ from usual diabetes consultations, which are scheduled similarly in the control group as compared to the transplantation group.

The major differences and strength between the present study and several others are as follows:

(a) this is the first long-term study comparing SIK or IAK transplantation and not ITA with a matched control-group
(b) follow-up of more than 7 years,
(c) precise prospective assessment of hypoglycemia in the transplant and control group,
(d) matched control group treated in the same fashion and by the same physicians as patients receiving an islet transplant.

The only comparable study to ours is the Vancouver Trial which included 21 patients with islet transplantation and 42 control patients, respectively, with a follow-up of 3 years, and a comparable difference in HbA1c between the groups in favor of islet transplantation. It was, however, conducted with ITA.[13,14] There is one 5-year follow-up study by Ryan et al[16] and a recent 3.4 years follow-up by Saito et al,[17] which showed a significant reduction of HbA1c and hypoglycemia after islet transplantation; however, both studies did not include a control group on intensive insulin therapy.

Insulin independence in our cohort is low compared to other centers because our program does not aim primarily to achieve insulin independence, but good glycemic control and avoidance of severe hypoglycemia.[5] Because of the low organ donation rate in Switzerland, islet isolations with a smaller islet mass are transplanted particularly in the setting of SIK and are very often sufficient to achieve the above goal. In this setting, there are few additional negative side effects of the transplanted islets (which are simultaneously transplanted with the kidney) for the patient (no risk of bleeding and immunosuppression is also needed for the transplanted kidney). In addition, the potent induction with thymoglobulin and tumor necrosis factor-α antagonists as described by Bellin et al.[11] were not used in this cohort because it was introduced later in our program.

Our study has some limitations. First, it is a prospective cohort study and not a randomized trial. Therefore, there are certain differences between the 2 groups (less diabetes specific complications, particularly better kidney function due to a better glycemic control in the control group). The ideal "control group" would have been patients with T1D who have received a KTA. However, at our institution, this patient group is very small because patients with T1D and kidney failure are always considered candidates for a combined islet-kidney or pancreas-kidney transplantation. As we have shown previously, patients with a KTA had an HbA1c between 8.4% and 9.0% during a 5-year follow-up after kidney transplantation.[9] Therefore, we considered patients treated with an intensified insulin regimen with the same diabetes duration to be the best alternative control group for comparison of various outcome parameters. Nevertheless, for HbA1c values and insulin requirement, we report data of 13 patients on the islet transplantation waiting list or patients who received combined pancreas-kidney transplantation, but lost function of the transplanted pancreas. These patients demonstrate similar HbA1c values as compared to the IIT control group, but a much higher insulin requirement, possibly due to the effects of immunosuppression. A randomized design for direct comparison is ethically not justifiable due to the well-known better outcome of combined islet-kidney or pancreas-kidney transplantation in comparison to KTA.[9]

Secondly, although the allograft follow-up of this study is much longer than that in previously published studies, it is still too short for evaluation of diabetic complications in these 2 patient groups. In addition, regression of advanced complications in the transplanted group (retinopathy, peripheral, and autonomic neuropathy) is highly unlikely.

In conclusion, to our knowledge, this is the first prospective cohort study in patients after SIK or IAK transplantation with a matched group on ITT with the same diabetes duration or patients on the waiting list for islet transplantation and a follow-up of more than 7 years, which demonstrates a significant improvement of glycemic control with a concurrent reduction of severe hypoglycemia with low additional costs.

ACKNOWLEDGMENTS

The authors thank E. Bernhard-Roth, M.T. Abbühl-Achermann, H. Seiler (all Division of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Zurich) and Thomas Fehr (Division on Nephrology, University Hospital Zurich) for their assistance.

REFERENCES

1. Maahs DM, West NA, Lawrence JM, et al. Epidemiology of type 1 diabetes. *Endocrinol Metab Clin North Am*. 2010;39:481–497.
2. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *The Diabetes Control and Complications Trial Research Group*. *N Engl J Med*. 1993;329:977–986.
3. Kyto JP, Harjutsalo V, Forsblom C, et al. Decline in the cumulative incidence of severe diabetic retinopathy in patients with type 1 diabetes. *Diabetes Care*. 2011;34:2005–2007.
4. Marshall SM. Diabetic nephropathy in type 1 diabetes: has the outlook improved since the 1980s? *Diabetologia*. 2012;55:2301–2306.
5. Lehmann R, Spinas GA, Moritz W, et al. Has time come for new goals in human islet transplantation? *Am J Transplant*. 2008;8:1096–1100.
6. Fioretto P, Steffes MW, Sutherland DE, et al. Reversal of lesions of diabetic nephropathy after pancreas transplantation. *N Engl J Med*. 1998; 339:69–75.
7. Thompson DM, Meloche M, Ao Z, et al. Reduced progression of diabetic microvascular complications with islet cell transplantation compared with intensive medical therapy. *Transplantation*. 2011;91:373–378.
8. Perez-Saez MJ, Toledo K, Navarro MD, et al. Long-term survival of simultaneous pancreas-kidney transplantation: influence of early posttransplantation complications. *Transplant Proc*. 2011;43:2160–2164.
9. Gerber PA, Pavlicek V, Demartines N, et al. Simultaneous islet-kidney vs pancreas-kidney transplantation in type 1 diabetes mellitus: a 5 year single centre follow-up. *Diabetologia*. 2008;51:110–119.
10. Fiorina P, Shapiro AM, Ricordi C, et al. The clinical impact of islet transplantation. *Am J Transplant*. 2008;8:1990–1997.
11. Bellin MD, Barton FB, Heitman A, et al. Potent induction immunotherapy promotes long-term insulin independence after islet transplantation in type 1 diabetes. *Am J Transplant*. 2012;12:1576–1583.
12. Shapiro AM, Lakey JR, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med*. 2000;343:230–238.
13. Fung MA, Warnock GL, Ao Z, et al. The effect of medical therapy and islet cell transplantation on diabetic nephropathy: an interim report. *Transplantation*. 2007;84:17–22.
14. Warnock GL, Thompson DM, Meloche RM, et al. A multi-year analysis of islet transplantation compared with intensive medical therapy on progression of complications in type 1 diabetes. *Transplantation*. 2008; 86:1762–1766.
15. Vantyghem MC, Marcelli-Tourvieille S, Fermon C, et al. Intraperitoneal insulin infusion versus islet transplantation: comparative study in patients with type 1 diabetes. *Transplantation*. 2009;87:66–71.
16. Ryan EA, Paty BW, Senior PA, et al. Five-year follow-up after clinical islet transplantation. *Diabetes*. 2005;54:2060–2069.
17. Saito T, Gotoh M, Satomi S, et al. Islet transplantation using donors after cardiac death: report of the Japan Islet Transplantation Registry. *Transplantation*. 2010;90:740–747.
18. Barton FB, Rickels MR, Alejandro R, et al. Improvement in outcomes of clinical islet transplantation: 1999–2010. *Diabetes Care*. 2012;35: 1436–1445.
19. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.
20. Lehmann R, Weber M, Berthold P, et al. Successful simultaneous islet-kidney transplantation using a steroid-free immunosuppression: two-year follow-up. *Am J Transplant*. 2004;4:1117–1123.
21. Lehmann R, Graziano J, Brockmann J, et al. Glycemic control in simultaneous islet-kidney versus pancreas-kidney transplantation in type 1 diabetes: a prospective 13-year follow-up. *Diabetes Care*. 2015; Feb 9 [Epub ahead of print].
22. Nordin C. The case for hypoglycaemia as a proarrhythmic event: basic and clinical evidence. *Diabetologia*. 2010;53:1552–1561.
23. Beckwith J, Nyman JA, Flanagan B, et al. A health economic analysis of clinical islet transplantation. *Clin Transplant*. 2012;26:23–33.
24. Greiner RA, Azoulay M, Brandle M. Estimation of direct medical cost of severe hypoglycemia in type 1 and type 2 diabetes patients in Switzerland (Abstract P-1592). 20th World Diabetes Conference, Montréal, 2009.